It Was Twenty Years Ago Today: How Omics Have Succeeded in Personalized Medicine

Mikhail Pyatnitskiy, PhD
Personalized medicine and omics: from bench to bedside
Omics publications: growth continues

Anda-Jáuregui & Hernández-Lemus, *Front in Oncol*, 2020
Personalized medicine and omics

Systematic analysis of 683 articles containing a definition of personalized medicine:

*PM seeks to improve stratification and timing of health care by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics*

Shtchleidgen et al. *BMC Medical Ethics*, 2013
[https://www.slideshare.net/osumedicalcenter/dr-leroy-hood-lecuture-on-p4-medicine](https://www.slideshare.net/osumedicalcenter/dr-leroy-hood-lecuture-on-p4-medicine)
Personalized medicine is genomics

76,326 genetic tests on GTR worldwide
37,289 tests belong to US laboratories

New genetic tests:
  62% diagnostic.
  11% risk assessment
  10% pre-symptomatic testing
  10% screening

Genomics became routine
Genomics: key applications

Pharmacogenomics
Individualize drug therapy
FDA: 80 biomarkers for 270 drugs

Rare diseases
Uncover previously unknown mutations
25-35% of undiagnosed patients, often with actionable findings

Newborn & inherited disease screening
Detect genetic disorder that may not manifest symptoms immediately
Crucial for family planning

Forensic genomics
Aid in criminal investigations, paternity testing, identifying human remains

Precision Oncology

Most successful area of pharmacogenomics
matching of cancer patients with targeted drugs

Several NGS-based multigene panels
Oncomine Dx, Foundation One CDx, MSK-IMPACT, PGDx elio

Clinical trials are on the way, results are somewhat mixed
SHIVA, IMPACT2, NCI-MPACT, TAPUR, NCI-MATCH, ...

Song et al., *Cancers*, 2023
Transcriptomics success story: MammaPrint®

- Assess the risk that a breast tumor will metastasize in five years
- 70 genes signature, correlation-based classifier
- Microarray, FFPE
- Supported by several clinical trials
- First results in 2002
- Similar tests: Oncotype DX, EndoPredict, Prosigna
Proteomics as an example of problems in translational medicine

How: use MS-based methods to detect ovarian cancer

Initial findings: several m/z peaks able to provide 100% sens, 95% spec, 94% PPV

Support: Adam et al., 2002; Drake et al., 2003; Petricoin et al., 2002b; Vlahou et al., 2001; Zhu et al., 2003

Planned to market: early 2004

But...

During the past 5 years, a large number of scientists were able to identify candidate protein disease biomarker profiles using patient research study sets and to achieve high diagnostic sensitivity and specificity in blinded test sets (1, 2, 5–8). Nevertheless, translating these research findings to useful and reliable clinical tests has been the difficult part. Clinical translation of promising ion fingerprints has been hampered by sample collection bias, interfering substances, biomarker perishability, laboratory-to-laboratory instrument variability, SELDI chip discontinuance and surface lot changes, and the stringent dependence of the ion signature on the subtleties of the reagent composition and incubation protocols. These difficulties are exemplified

Liotta & Petricoin, Clin Chemistry, 2008
Epigenomics: seems promising, but...

- Most approved assays measure methylation of few genes: Epi proColon (SEPT9), ColoGuard (BMP3, NDRG4)

- Several new promising assays in development: HelioLiver (28 genes), Bladder EpiCheck (15 markers), EPICUP (Illumina 450k)

- Massive increase in number of CTs involving methylation in oncology (focus on colorectal cancer)

- Epigenetic clocks: promising, but still not in clinics
Multiomics: foundation of systems medicine

Babu & Snyder, *Mol Cell Proteomics*, 2023
integrative Personal Omics Profile (iPOP aka Snyderome)

- Multiomics longitudinal profile, 14 months, 20 timepoints for 54 yo Caucasian male, BMI=23.9
- Two viral infections: human rhinovirus (HRV) and a respiratory syncytial virus (RSV)
- Genetic disease risks (RiskOGram algorithm): glaucoma, basal cell carcinoma, hypertriglyceridemia, and Type 2 Diabetes (T2D)

Conclusions:
- Clinical utility
- continuous glucose monitoring
genomics
transcriptomics, metabolomics

Pre- and post-test probability (after incorporating WGS data)
Num disease-associated SNVs for risk calculation

Chen et al., *Cell*, 2012
Pioneer 100 Wellness Project

- 108 individuals (ages 21-89), 9 months, 3 rounds followed by coaching sessions
- WGS, proteomics, metabolomics, gut microbiome, wearables
- In each round: 218 lab tests, 643 metabolites, 262 proteins, 127 polygenic scores, 4616 OTUs
Results: correlations, correlations, correlations

The polygenic score for inflammatory bowel disease is negatively correlated with cystine.

Polygenic risk scores correlate with blood analytes.

Price et al., Nat Biotechnol, 2017
For each out-of-range measurement the coach would recommend lifestyle changes.

Individual recommendations categories: diet, exercise, stress management, dietary supplements, or physician referral.

Most significant improvements: vitamin D, mercury, HbA1c, total cholesterol, IL-8.

Ex: 65-year-old male, revealed high ferritin level in blood, homozygous for HFE C282Y, the primary risk factor for hereditary hemochromatosis. Therapeutic phlebotomy recommended. Ferritin level remained normal throughout the remainder of the study.

### Clinical laboratory test

<table>
<thead>
<tr>
<th>Health area</th>
<th>Name</th>
<th>N</th>
<th>Δ per round</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition</td>
<td>Vitamin D</td>
<td>95</td>
<td>+7.2 ng/mL/round</td>
<td>7.1 x 10⁻²⁵</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Mercury</td>
<td>81</td>
<td>-0.002 mcg/g/round</td>
<td>8.9 x 10⁻⁹</td>
</tr>
<tr>
<td>Diabetes</td>
<td>HbA1c</td>
<td>52</td>
<td>-0.085%/round</td>
<td>9.2 x 10⁻⁶</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>LDL particle number (Quest)</td>
<td>30</td>
<td>+130 nmol/L/round</td>
<td>9.3 x 10⁻⁵</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Methylmalonic acid (Genova)</td>
<td>3</td>
<td>-0.49 mmol/mol creatinine/round</td>
<td>2.1 x 10⁻⁴</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>LDL pattern (A or B)</td>
<td>28</td>
<td>-0.16/round</td>
<td>4.8 x 10⁻⁴</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Interleukin-8</td>
<td>10</td>
<td>-6.1 pg/mL/round</td>
<td>5.9 x 10⁻⁴</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Total cholesterol (Quest)</td>
<td>48</td>
<td>-6.4 mg/dL/round</td>
<td>7.2 x 10⁻⁴</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>LDL cholesterol</td>
<td>57</td>
<td>-4.8 mg/dL/round</td>
<td>8.8 x 10⁻⁴</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>LDL particle number (Genova)</td>
<td>70</td>
<td>-69 nmol/L/round</td>
<td>1.2 x 10⁻³</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Small LDL particle number (Genova)</td>
<td>73</td>
<td>-56 nmol/L/round</td>
<td>3.5 x 10⁻³</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fasting glucose (Quest)</td>
<td>45</td>
<td>-1.9 mg/dL/round</td>
<td>8.2 x 10⁻³</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Total cholesterol (Genova)</td>
<td>43</td>
<td>-5.4 mg/dL/round</td>
<td>1.2 x 10⁻²</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Insulin</td>
<td>16</td>
<td>-2.3 IU/mL/round</td>
<td>1.5 x 10⁻²</td>
</tr>
<tr>
<td>Inflammation</td>
<td>TNF-alpha</td>
<td>4</td>
<td>-6.6 pg/mL/round</td>
<td>1.8 x 10⁻²</td>
</tr>
<tr>
<td>Diabetes</td>
<td>HOMA-IR</td>
<td>19</td>
<td>-0.56/round</td>
<td>2.0 x 10⁻²</td>
</tr>
</tbody>
</table>
Translational omics: seems we are not very good

Davalos & Esteller, CA Cancer J Clin, 2023

Maybe we’re searching in the wrong place

“Biomedical scientists are addicted to data like alcoholics are addicted to cheap booze”

Director, MIT Center for Precision Cancer Medicine

Prof. M. Yaffe

- Focus on deep phenotyping? Lifestyle and environment are very important

- Not only cancer?

McMoll et al., Clin Pharm & Ther., 2019
Tebani et al., IJMS, 2016
Variability of omics profiles

Multi-omics profiles measured 6 months apart in 156 healthy children from 5 countries
Adjusting for various explanatory variables for inter-individual and intra-individual variation

Conclusions:
• Intra-individual variation accounts for the largest part of total variation
• The less stable omics: gene expression. Should be used to assess individual trajectories
• More stable omics: DNA methylation and serum metabolites. Should be used as biomarkers

Variability of omics profiles in healthy populations remains under-studied

Gallego-Pauls et al., *BMC Medicine*, 2021
Reproducibility crisis

Freedman et al, Plos Biol, 2015
How to cheat with your analysis: some bad advices

- Remember, everybody (editors, reviewers, investors) prefers positive results.
- Always be your own judge, jury and executioner (the self-assessment trap)
- P-hacking is great: your boss will stay satisfied
- Diffuse author’s responsibility (“brotherly graves”)
- Do not disclose intricacies of the conducted analysis

https://xkcd.com/1478/
“If you torture the data long enough, it will confess to anything.”

- Ronald Coase,
Nobel Prize winning economist
AI is our new hope

Subramanian et al., J Transl Med., 2020
customers' assessments of Watson for Oncology that say it produced "often inaccurate" recommendations that pose "serious questions about the process for building content and the underlying technology."

"While Watson for Oncology provides safe treatment options, treatment decisions ultimately require the involvement and clinical judgement of the treating physician... No technology can replace a doctor and his or her knowledge about their individual patient."

https://spectrum.ieee.org/biomedical/diagnostics/how-ibm-watson-overpromised-and-underdelivered-on-ai-health-care
https://www.statnews.com/2017/09/05/watson-ibm-cancer/
Characteristics of successful omics studies

Glaab et al., *BMJ Open*, 2021

Scoping review of 352 biomarker discovery studies using ML analysis of omics data

- **Study design & sample size**: statistical power, balanced groups, batch effect avoidance
- **Statistical evaluation**: cross-validation, external cohorts, multiple testing correction
- **Clarity of scope & goals**: inclusion/exclusion criteria, primary/secondary outcome
- **Documentation**: reproducible method description
- **Model interpretability**: biological plausibility, human-interpretable models
- **Integration of prior knowledge**: pathways & networks, clinical and real-world data

<table>
<thead>
<tr>
<th>Name</th>
<th>Test approval type</th>
<th>Purpose (data type used for discovery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ColoPrint</td>
<td>LDT</td>
<td>Colon cancer development of distant metastasis prediction (DNA microarray gene expression data).</td>
</tr>
<tr>
<td>Prosigna/PAM50</td>
<td>FDA-cleared Assay</td>
<td>Breast cancer risk of distant recurrence prediction (DNA microarray gene expression data).</td>
</tr>
<tr>
<td>Decipher</td>
<td>LDT</td>
<td>Prostate cancer metastatic risk prediction (DNA microarray gene expression data).</td>
</tr>
<tr>
<td>Cancer Type ID</td>
<td>LDT</td>
<td>Predict tumour type for cancers of unknown / uncertain diagnosis (DNA microarray gene expression data).</td>
</tr>
<tr>
<td>Afirma Gene Expression</td>
<td>LDT</td>
<td>Discriminate between benign and cancerous thyroid nodules (DNA microarray gene expression data).</td>
</tr>
<tr>
<td>Classifier</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foundation One Heme</td>
<td>LDT</td>
<td>Test for haematologic malignancies, sarcomas or solid tumours (RNA and DNA sequencing data).</td>
</tr>
<tr>
<td>PGDx Elio Tissue Complete</td>
<td>FDA-cleared Assay</td>
<td>Test to assess somatic mutations and tumour mutation burden for solid tumours (DNA sequencing data).</td>
</tr>
<tr>
<td>AlloMap Heart</td>
<td>FDA-cleared Assay</td>
<td>Identifying heart transplant recipients with risk of cellular rejection (DNA microarray gene expression data).</td>
</tr>
<tr>
<td>Corus CAD</td>
<td>LDT</td>
<td>Identify obstructive coronary artery disease (DNA microarray gene expression data).</td>
</tr>
<tr>
<td>Vectra DA</td>
<td>LDT</td>
<td>Multibiomarker blood test for rheumatoid arthritis (immunassyay- clinical data, 996 candidate biomarkers derived from integrative data analysis).</td>
</tr>
<tr>
<td>Helix Laboratory Platform &amp; Health Risk App for Late-onset Alzheimer’s</td>
<td>FDA-cleared medical device</td>
<td>Whole exome sequencing constituent device based for reporting and interpreting general genetic health risks (DNA sequencing data).</td>
</tr>
</tbody>
</table>
Some conclusions

- Early promises turned out to be overly optimistic (as usual). Seems most low-hanging fruits are already picked.
- There should be clinical evidences of whether -omics approach is better than traditional methods.
- There should be more -omics in medical education.
- A bright future lies ahead, let’s get to work!